CONSENSUS CLINICAL DATA STANDARDS FOR ALZHEIMER'S DISEASE: FOCUS ON PREVENTION TRIALS

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BACKGROUND: Alzheimer's disease clinical trials targeting the presymptomatic stages rely on the appropriate use of biomarkers and outcome measures for accurate decision making. Reliable and reproducible methodologies to assure confidence in biomarker implementation is facilitated by adoption of clinical data standards that can be employed throughout the duration of the lengthy trial. Critical Path Institute's Coalition Against Major Diseases (CAMD) in partnership with the Banner Alzheimer's Prevention Initiative (API) aims to enable the use of Clinical Data Interchange Standards Consortium (CDISC) consensus data standards in two key ongoing AD amyloid modifying treatment trials. It is important to think of these standards as fulfilling two purposes. An intuitive one is the remapping of existing data for aggregation purposes, but more importantly, the prospective collection of data in standardized form is also critical, not just to seamlessly integrate additional data into aggregated databases, but also for simplifying regulatory submissions. In Alzheimer's disease clinical trials, there is an urgent need for sponsors to understand key parameters of data standards that are required to capture and record particularly at the early stages of planning of the long costly trials.

METHODS: A coalition of academic experts, industry members, regulatory agencies, in conjunction with ADNI leaders collectively developed data standards in partnership with CDISC that included brain imaging, cerebrospinal fluid (CSF), and cognitive endpoints. With input from clinical subject matter experts (SMEs), working groups of data standards experts mapped clinical concepts relevant to AD to the CDISC Study Data Tabulation Model (SDTM) and developed controlled terminology to support the construction of standardized databases for research and regulatory submission in AD clinical trials. These standards were reviewed with respect to prevention trials with a focus on the following biomarkers: imaging (structural/MRI, PET) and CSF analytes. Specific concepts were reviewed and those parameters that should be defined at the planning and acquisition phase of clinical trials were extracted.

RESULTS:
Comprehensive and thorough review of the AD CDISC standard therapeutic area user guide (TAUG) selectively identified core domains that are relevant at the acquisition phase of AD trials. Key concepts identified with respect to MRI include specific image acquisition parameters such as pulse sequences, image weighting, and magnet strength. For PET or PET/CT, the concepts identified include radiolabeled tracer used, uptake time, time of scan, anatomical region-of-interest and reference anatomical location (for SUVR), and various parameters relevant to image acquisition and correction

For all types of imaging, scanner identification and software versions (scanner operating system and analysis software) are also important to capture. For cerebrospinal fluid (CSF) biomarkers, the relevant parameters identified include time and date of lumbar puncture, specific anatomical location of lumbar puncture (L3-L4 intervertebral space), gauge of spinal needle and storage tube type. A comprehensive list of all parameters relevant to imaging and CSF that were identified as factors to capture were defined and shared with CAMD member sponsors of the two prevention API trials. Items in biomarkers and cognitive outcome measures for the prevention trials that are not captured in the AD v2.0 standards are being targeted to incorporate in future revisions to the AD data standards.

CONCLUSIONS:
The use of consensus data standards maximizes efficiency in regulatory review and facilitates analyses across diverse studies. Importantly, CDISC standards will be required by FDA for regulatory submission as early as fiscal year 2017. These standards foster the collection of clinical trial data and the integration and analysis of existing or anticipated data across various stakeholders' systems independent of the particular platform. It's important that sponsors plan to employ the use of key elements described by the AD CDISC standards at the onset of the study and even prior to study initiation to ensure poolable data are produced, to maximize efficiency, and to streamline regulatory review. Finally the use of AD CDISC standards serves to maximize the ability to analyze across distinct AD trials in the future. The AD CDISC TAUG is readily available to sponsors, data scientists and researchers for wide implementation (http://www.cdisc.org/therapeutic).